Propagation of perturbations in protein binding networks

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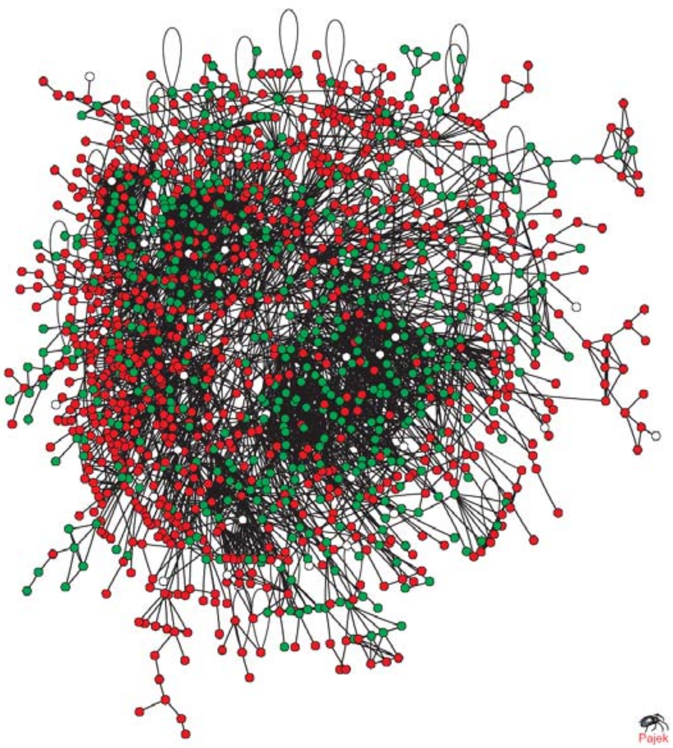
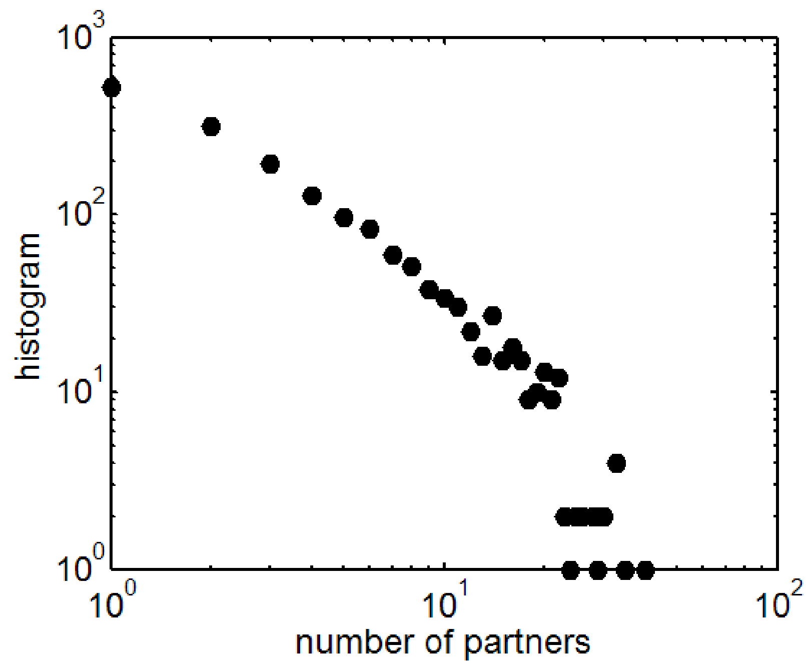




- Experimental interaction data are binary instead of graded → it is natural to study topology
  - Very heterogeneous number of binding partners (degree)
  - One large cluster containing ~80% proteins
  - Perturbations were analyzed from purely topological standpoint
- Ultimately one want to quantify the equilibrium and dynamics: time to go beyond topology!

Law of Mass Action equilibrium

- $dD_{AB}/dt = r^{(on)}_{AB} F_A F_B - r^{(off)}_{AB} D_{AB}$
- In equilibrium $D_{AB}=F_A F_B/K_{AB}$ where the dissociation constant $K_{AB}= r^{(off)}_{AB}/ r^{(on)}_{AB}$ has units of concentration
- Total concentration = free concentration + bound concentration $\rightarrow$ $C_A= F_A+F_A F_B/K_{AB} \rightarrow$ $F_A=C_A/(1+F_B/K_{AB})$
- In a network $F_i=C_i/(1+\Sigma_{\text{neighbors } j} F_j/K_{ij})$
- Can be numerically solved by iterations

What is needed to model?

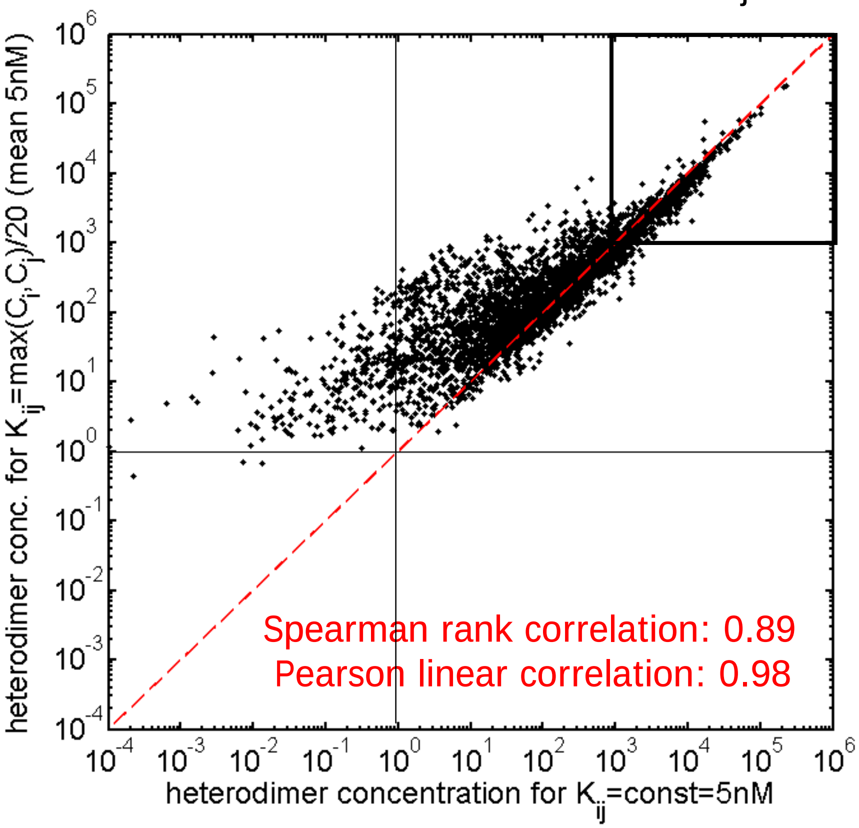
- A reliable network of reversible (non-catalytic) protein-protein binding interactions
  - √ CHECK! e.g. physical interactions between yeast proteins in the BIOGRID database with 2 or more citations. Most are reversible: e.g. only 5% involve a kinase
- Total concentrations C_i and sub-cellular localizations of all proteins
  - √ CHECK! genome-wide data for yeast in 3 Nature papers (2003, 2003, 2006) by the group of J. Weissman @ UCSF.
  - VERY BROAD distribution: C_i ranges between 50 and 10^6 molecules/cell
  - Left us with 1700 yeast proteins and ~5000 interactions
- *in vivo* dissociation constants K_{ij}
  - OOPS! ☹. High throughput experimental techniques are not there yet

Let's hope it doesn't matter

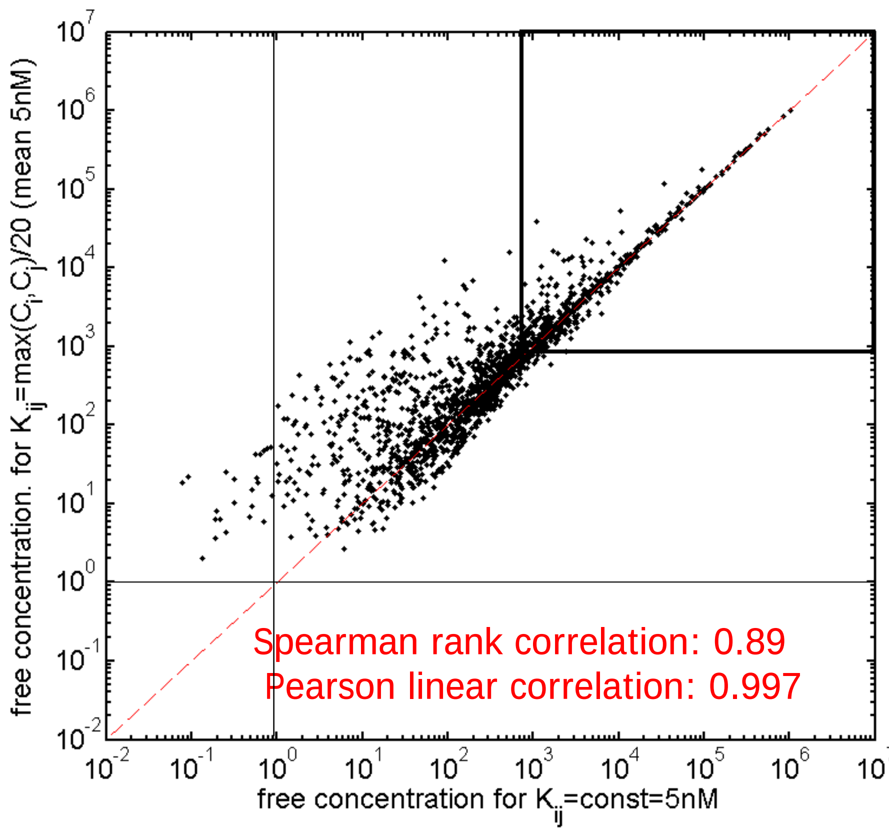
- The overall binding strength from the PINT database: $<1/K_{ij}>=1/(5nM)$. In yeast: 1nM ~ 34 molecules/cell
- Simple-minded assignment K_{ij}=const=10nM (also tried 1nM, 100nM and 1000nM)
- Evolutionary-motivated assignment: $K_{ij}=\max(C_i,C_j)/20$: K_{ij} is only as small as needed to ensure binding given C_i and C_j
- All assignments of a given average strength give ROUGHLY THE SAME RESULTS

Robustness with respect to assignment of K_{ij}

Bound concentrations: D_{ij}



Free concentrations: F_i



Numerical study of propagation of perturbations

- We simulate a twofold increase of the abundance C_0 of just one protein
- Proteins with equilibrium free concentrations F_i changing by >20% are significantly perturbed
- We refer to such proteins i as concentration-coupled to the protein 0
- Look for cascading perturbations

Resistor network analogy

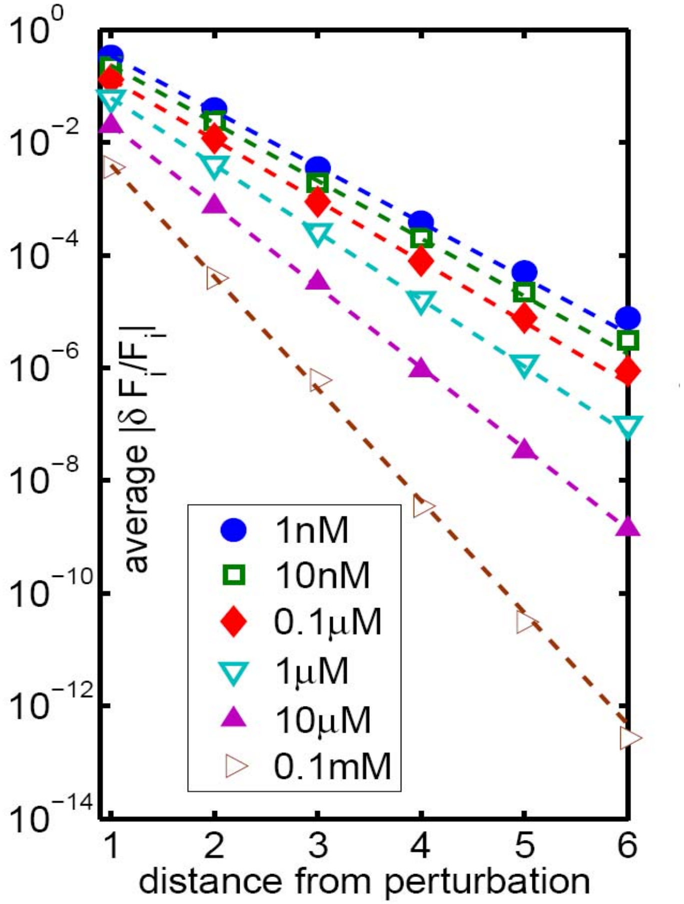
- Conductivities σ_{ij} – dimer (bound) concentrations D_{ij}
- Losses to the ground σ_{iG} – free (unbound) concentrations F_i
- Electric potentials – relative changes in free concentrations $(-1)^L \delta F_i/F_i$
- Injected current – initial perturbation δC_0

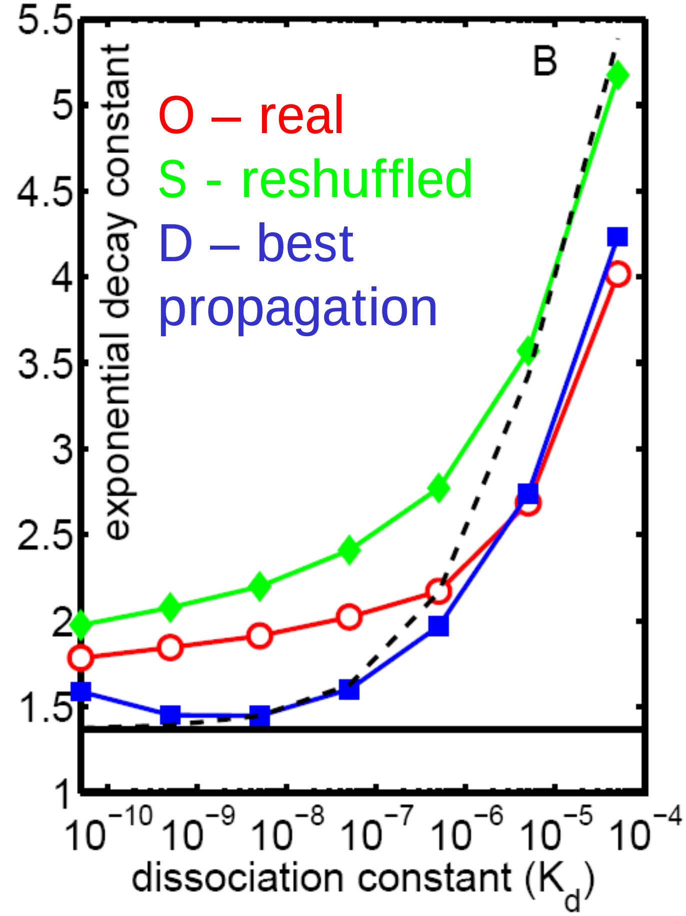
SM, K. Sneppen, I. Ispolatov, arxiv.org/abs/q-bio.MN/0611026;

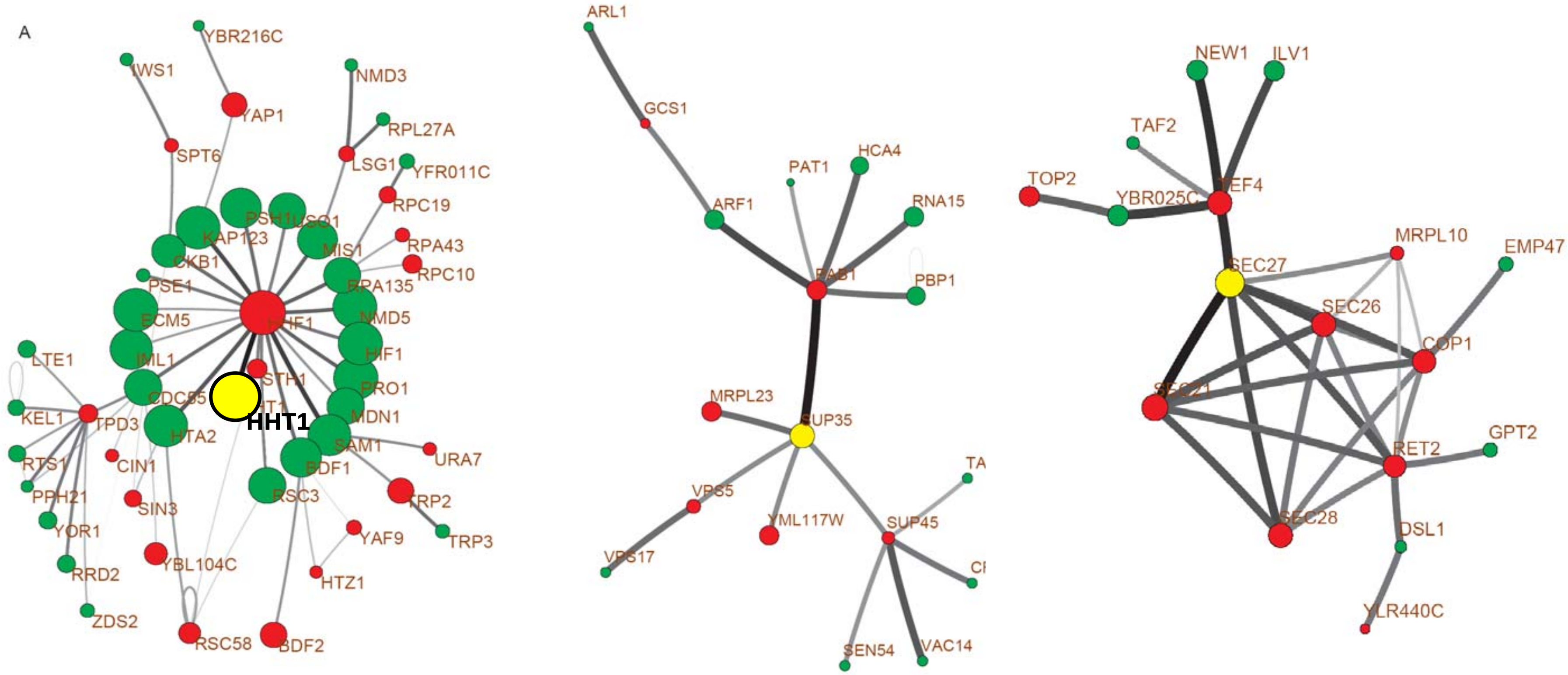
What did we learn from this mapping?

- The magnitude of perturbations` exponentially decay with the network distance (current is divided over exponentially many links)
- Perturbations tend to propagate along highly abundant heterodimers (large σ_{ij})
- F_i/C_i has to be low to avoid “losses to the ground”
- Perturbations flow down the gradient of C_i
- Odd-length loops dampen the perturbations by confusing $(-1)^L \delta F_i/F_i$

Exponential decay of perturbations



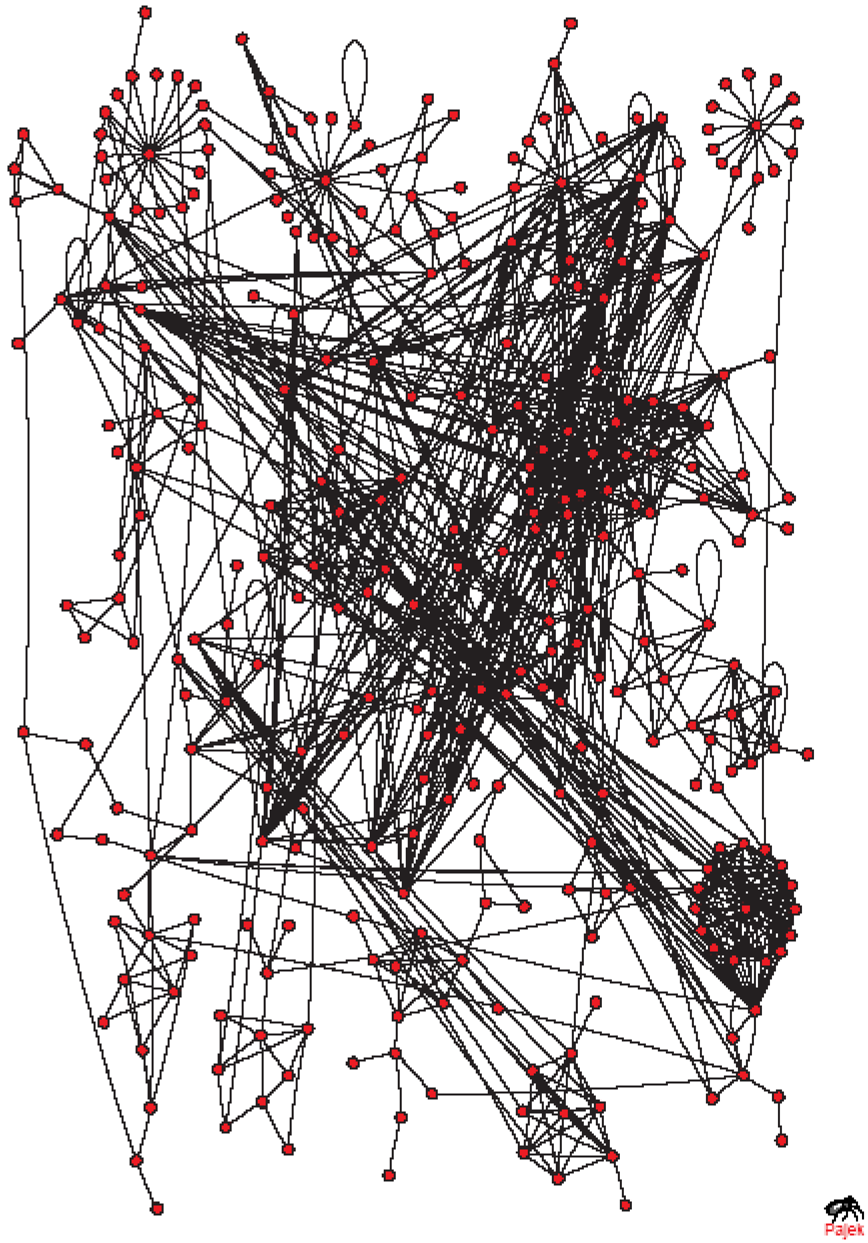


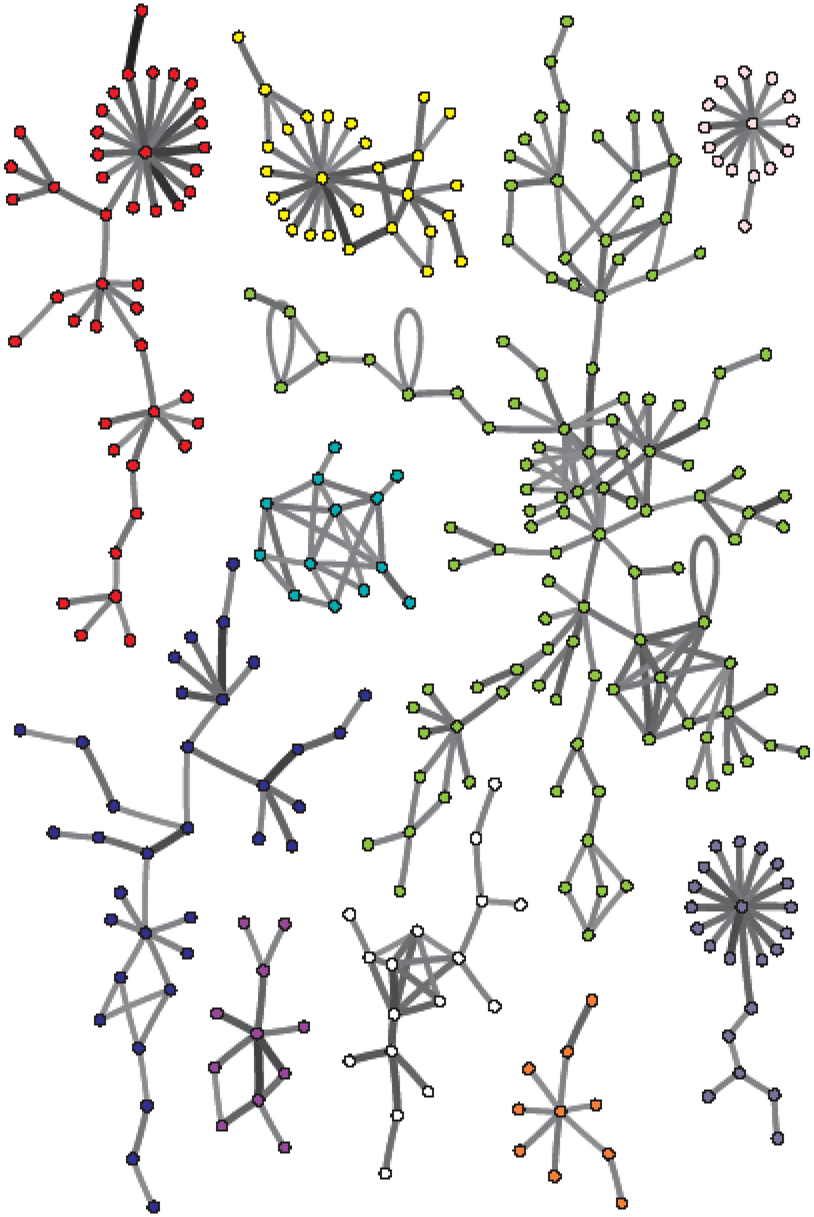


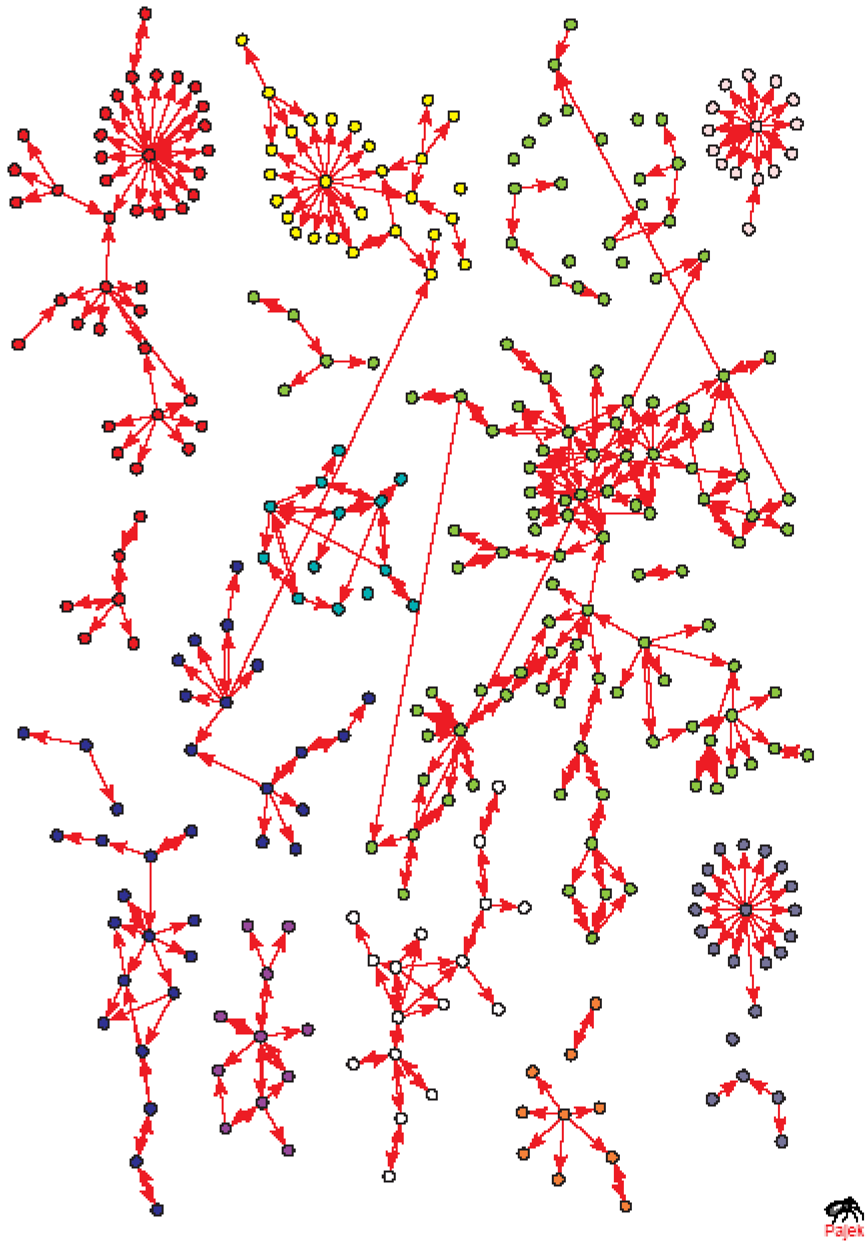
L	variable K_{ij}, mean= 5nM	constant $K_{ij} = 1$nM	constant $K_{ij} = 10$nM	constant $K_{ij} = 0.1\mu$M	constant $K_{ij} = 1\mu$M	all pairs at distance L
1	2003	2469	1915	1184	387	8168
2	415	1195	653	206	71	29880
3	15	159	49	8	0	87772
4	2	60	19	0	0	228026
5	0	3	0	0	0	396608

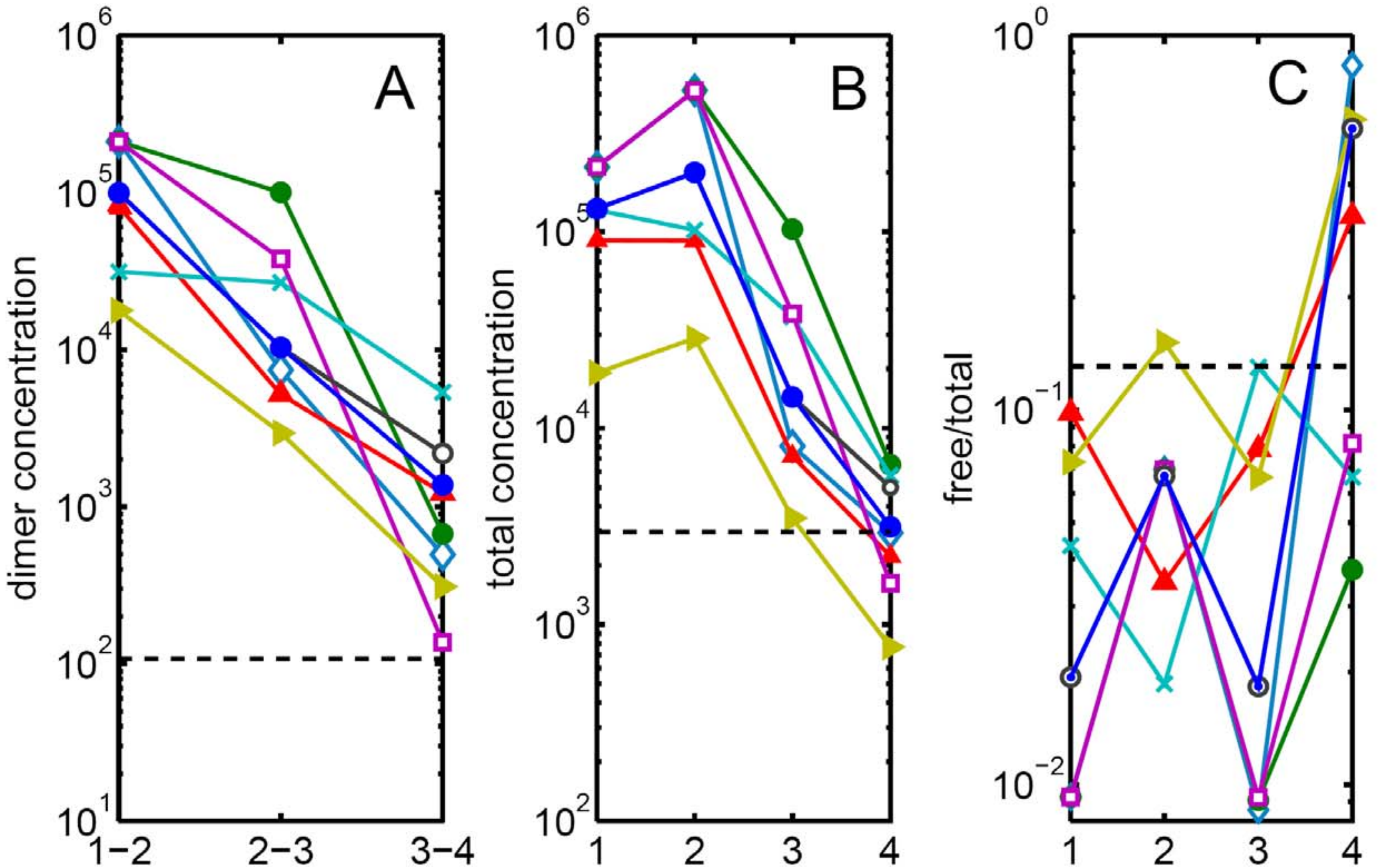
SM, I. Ispolatov, PNAS in press (2007)

What conditions
make some
long chains
good conduits
for propagation of
concentration perturbations
while suppressing it
along side branches?






Pajek



- Perturbations propagate along dimers with large concentrations
- They cascade down the concentration gradient and thus directional
- Free concentrations of intermediate proteins are low

SM, I. Ispolatov, PNAS in press (2007)

Implications of our results

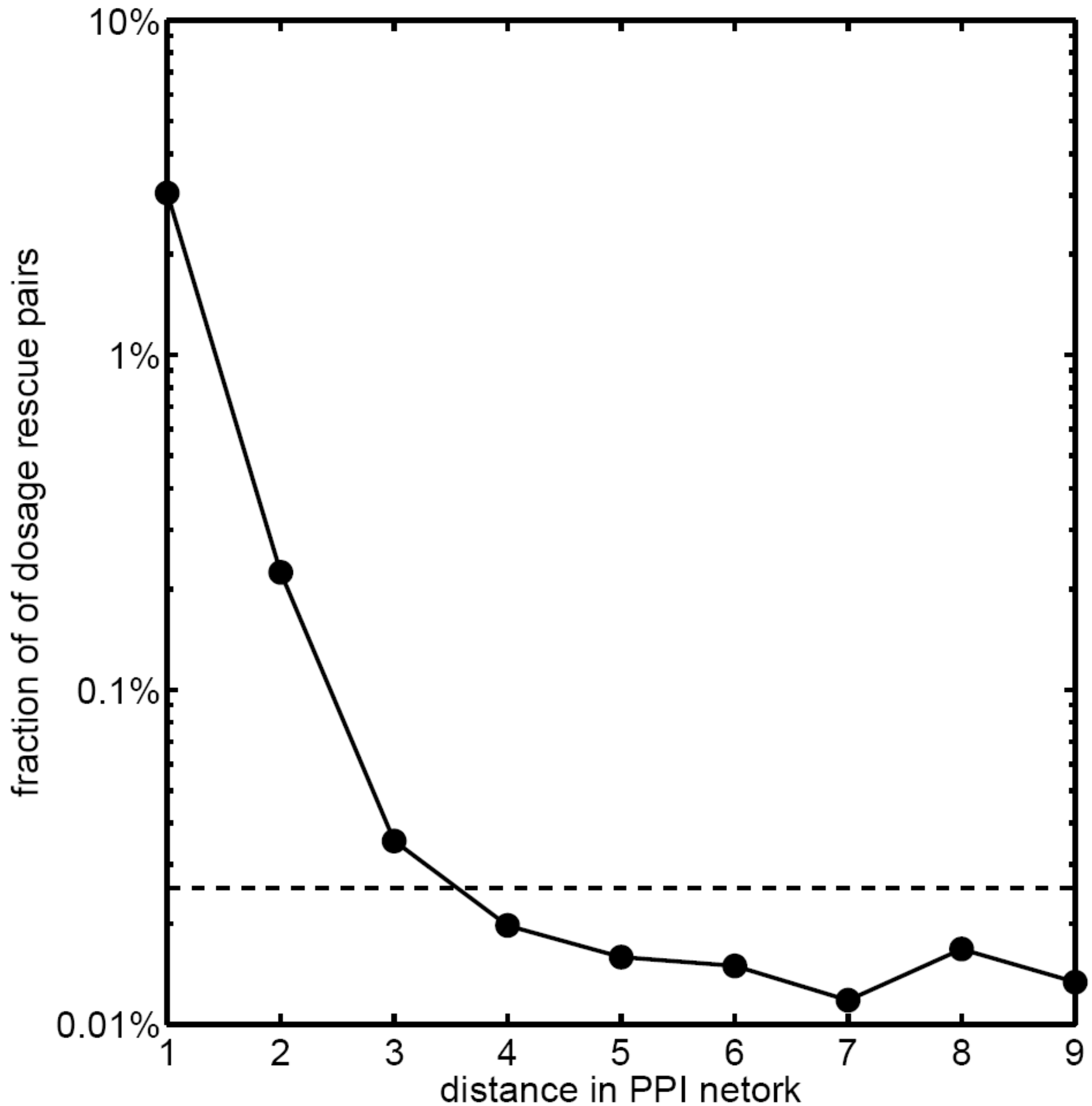
Cross-talk via small-world topology is suppressed, but...

- Good news: on average perturbations via reversible binding rapidly decay
- Still, the absolute number of concentration-coupled proteins is large
- In response to external stimuli levels of several proteins could be shifted. Cascading changes from these perturbations could either cancel or magnify each other.
- Our results could be used to extend the list of perturbed proteins measured e.g. in microarray experiments

Genetic interactions

- Propagation of concentration perturbations is behind many genetic interactions e.g. of the “dosage rescue” type
- We found putative “rescued” proteins for 136 out of 772 such pairs (18% of the total, P-value 10^{-216})

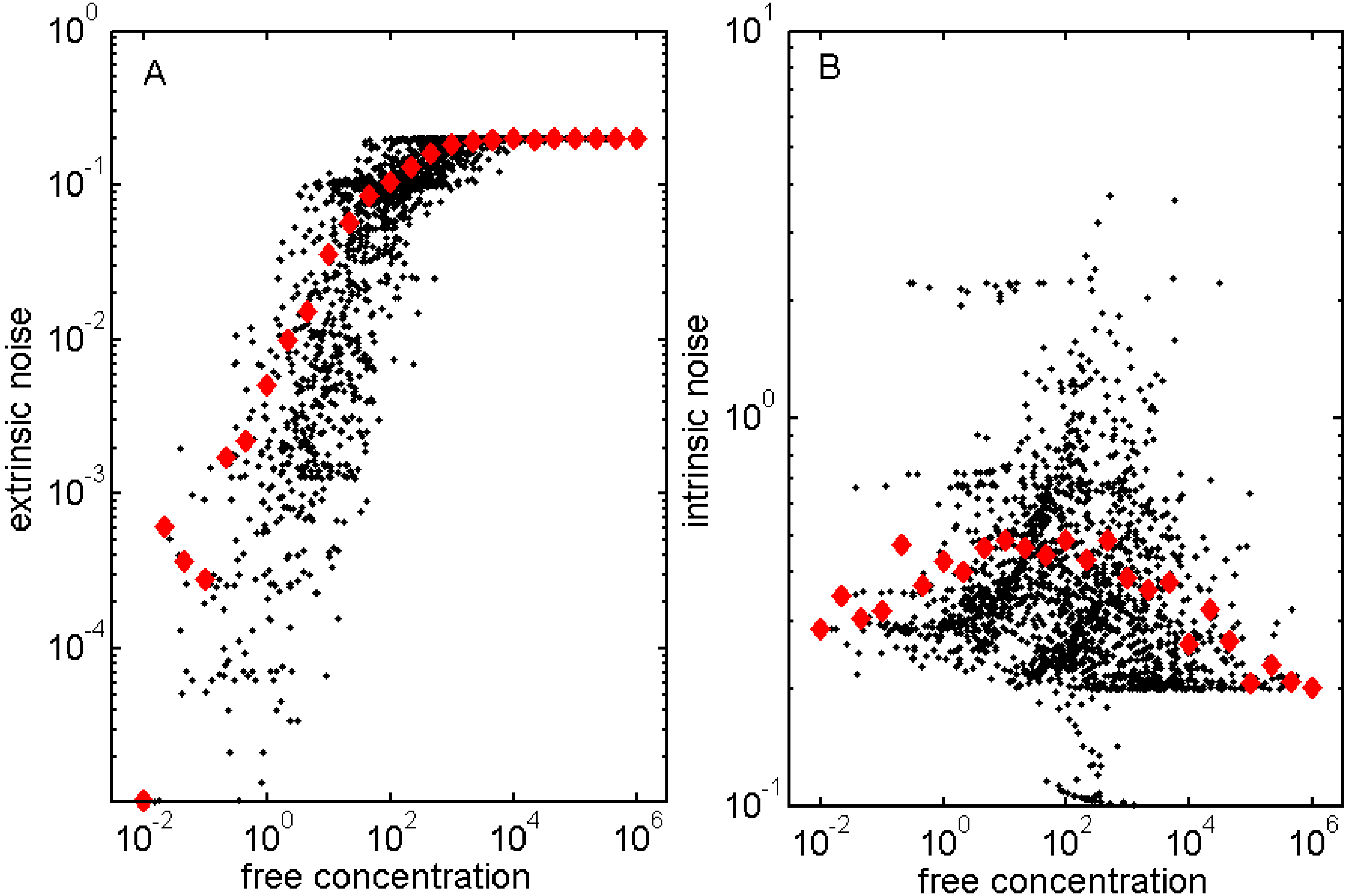
SM, I. Ispolatov, PNAS in press (2007)



SM, I. Ispolatov, PNAS in press (2007)

Intra-cellular noise

- Noise is measured for total concentrations C_i (Newman et al. Nature (2006))
- Needs to be converted in biologically relevant bound (D_{ij}) or free (F_i) concentrations
- Different results for intrinsic and extrinsic noise
- Intrinsic noise could be amplified (sometimes as much as 30 times!)



A
B
extrinsic noise
intrinsic noise
free concentration
free concentration
10^0
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^1
10^0
10^{-1}
10^{-2}
10^0
10^2
10^4
10^6

Could it be used for regulation and signaling?

- 3-step chains exist in bacteria: anti-anti-sigma-factors → anti-sigma-factors → sigma-factors → RNA polymerase
- Many proteins we find at the receiving end of our long chains are global regulators (protein degradation by ubiquitination, global transcriptional control, RNA degradation, etc.)
  - Other (catalytic) mechanisms spread perturbations even further
  - Feedback control of the overall protein abundance?

Future work

Kinetics
Non-specific vs specific

- How quickly the equilibrium is approached and restored?
- Dynamical aspects of noise

- How specific interactions peacefully coexist with many non-specific ones

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THE END